UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/380,419	07/24/00	ROTHSCHILD	M P03815US1

022885 HM12/0619
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EXAMINER	
EINSMANN,J	
ART UNIT	PAPER NUMBER
1655	15

DATE MAILED: 06/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/380,419	ROTHSCHILD ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 and 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Priority

1. Priority is granted in this case to the instant filing date. Although the cited provisional applications contain disclosure of the polymorphism used in the instant methods, they do not provide adequate support for the instantly claimed screening methods.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s):

(A) The sequence identifiers in the examples do not match up with those provided in the sequence listing. For example, the sequence identified in the examples as SEQ ID NO: 6 (on page 19, for example) is different from SEQ ID NO: 6 in the sequence listing.

(B) The sequences recited in Fig. 7 need to be identified with proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant correct the discrepency between the examples and the sequence listing. If applicant chooses to submit a new CRF and paper copy, Applicant must submit a new CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12, 20-23, and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying a pig which possesses a genotype indicative of the pig having less back fat than pigs with a different genotype, indicative of the pig having a lower daily gain that pigs with a different genotype, or of the pig having a lower feed intake than a pig with a different genotype, wherein said method comprises screening DNA of the pig for a G → A point mutation at position 678 of SEQ ID NO: 1 (of the sequence listing) and wherein the absence of the mutation is indicative of a pig having the recited traits, does not reasonably provide enablement for methods which screen other animals or methods which utilize other polymorphisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The prior art teaches one polymorphism in humans which is associated with obesity (Yeo *et al.* 1998. Nature Genetics, Vol. 20, p. 111-112). Methods for screening humans using this polymorphism are also enabled.

Each of the rejected claims are broadly drawn to include at least one of the following: methods for screening any animal or methods for using any polymorphism in the MC4R gene.

The specification provides a single working example which demonstrates that in pigs homozygous for an G point mutation at position 678 of SEQ ID NO: 1 is correlated with pigs that have less backfat, lower daily gain, and lower feed intake than pigs homozygous for an A at

position 678. The prior art is silent with respect to other possible polymorphisms in the MC4R gene or with respect to the association of this particular polymorphism with any metabolic trait in any other animal. Neither the specification nor the prior art provide evidence of any universal correlation between polymorphisms in MC4R and metabolic traits which would conclusively associate the polymorphism instantly disclosed with metabolic traits in any other animal.

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. The amount of direction or guidance presented in the specification and the prior art of only one point mutation in the MC4R gene of one species of animal is minimal, given that just the redundancy of the genetic code would allow for several thousand different sequences wh en conserved or non-conserved mutations are considered, millions of different sequences for the pig MC4R gene may exist which may, or may not, have substantial functional differences or association with the traits of interest herein. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art.

Furthermore, there is no evidence in the specification provided that the identified polymorphism is causative of the observed traits. This is a significant absence of evidence, since it is possible that the polymorphism is merely a marker for the causative genotype. In light of the fact that the causative genotype has not been identified, it is unpredictable as to whether or not markers which are linked to the instantly disclosed polymorphism would be informative for the traits of interest herein (for example, as claimed in claims 29 and 30).

Although the level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), the quantity of experimentation that would be necessary to

determine even one additional polymorphism in the pig MC4R gene is substantial since there is no predictability for which sequences exist which code for polymorphisms in pig MC4R genes. Applicants have not disclosed how one would go about detecting additional polymorphisms associated with the traits of interest herein. Because there is no reason to expect that any additional polymorphism is associated with the instantly discussed metabolic traits and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators of these traits would require the rearing and subsequent slaughtering of many, many pigs in order to analyze their metabolic traits and in order to screen the MC4R gene for informative polymorphisms. There is no evidence, however, of any frequency of significant polymorphisms. Further, even if polymorphisms were detected, the polymorphism may not correlate to polymorphic traits. The instantly disclosed polymorphism may be coincident with and unrelated to a different, unlinked (on the chromosome) polymorphism such as another MC4R polymorphism or a polymorphism in an undetermined gene that actually determines the metabolic traits. The instantly disclosed polymorphism would not have any meaning or effect, but might appear to influence metabolic traits due to it's close proximity to some other gene.

Furthermore, the level of unpredictability and the level of experimentation required to expand the instantly disclosed methods to include animals of other species are also quite high. There is no teaching in the specification that the disclosed polymorphism even exists in animals of other species. Since there is not evidence that the disclosed polymorphism is causative of the traits (as discussed above), it is highly unpredictable as to whether the polymorphism would mark the same traits in other animals. Further, in order to provide such evidence the skilled artisan would be required to undertake extensive studies of the metabolic traits of hundreds upon

hundreds of different individual animals of each of many different species of animal. Such experimentation would be inventive in itself.

Due to the broad nature of the claims, the presence of only one working example, the extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

4. Claims 10, 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 10 includes an amplification step which requires amplifying an entire MC4R gene. Claims 24-26 are drawn to kits which comprise a reagent that identifies a polymorphism in a MC4R gene. This rejection applies to these claims in so far as they encompass primers that amplify the any MC4R gene or some fragment thereof, or primers that amplify the entire MC4R gene from any animal except humans. The specification has taught only a 746 base pair fragment of the porcine MC4R gene (SEQ ID NO: 1 of the sequence listing). The human MC4R gene is known in the prior art (Yamada *et al.* (US 5703220)). No other animal MC4R genes have been disclosed in either the instant specification or the prior art. Thus, applicant has express possession of only primers whose sequences are sub-fragments of SEQ ID NO: 1. It is further noted that these kits are not limited such that they amplify the specific polymorphism taught in the instant specification.

With regard to the written description, these claims encompass nucleic acid sequences different from those disclosed in the specific SEQ ID No:s. For example, with regard to the porcine MC4R gene, the claims encompass primers that flank SEQ ID NO: 1 but would retain the ability to amplify the polymorphism at nucleotide 678 of SEQ ID NO: 1. Further, these claims encompass nucleic acids which would amplify other, undisclosed, polymorphisms, and nucleic acids which would amplify the MC4R gene of other species.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only SEQ ID NO: 1 is described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any reagent for detecting polymorphisms, known and unknown in any MC4R which has nucleic acids modified by addition, insertion, deletion, substitution or inversion with the disclosed SEQ ID Nos but retaining correlative function in the claimed product.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim1-23 and 26-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13, 20-23, and 29-31 are indefinite for failing to recite a final process step which agrees back with the preamble. For example, claims 1-13 are drawn to a method for identifying an animal which possesses a genotype indicative of the metabolic traits, yet the claims recite a final step of identifying a polymorphism. The claims do not set forth the relationship between the identifying a polymorphism and the identifying an animal and therefore, it is not clear whether the claims are intended to be drawn to a method for identifying an animal or a method for identifying an polymorphism.

Claims 1-13, 20-23, and 31-32 are indefinite over the recitation of "possesses a genotype indicative of the metabolic traits of fat content, growth rate, and feed consumption" because it is not clear what the genotype is indicating. That is, the claims seem to suggest that the genotype indicates that the animals have these traits, however, it also seems that all animals have these traits to some degree or another. Therefore, it is not clear what is meant by this phraseology.

Claims 2, 4-6, and 28 are indefinite over the recitation of "polymorphism is characterized by a nucleotide position" because this phrase does not clearly define the polymorphism. It is not clear what is meant when a polymorphism is characterized by a nucleotide position.

Claims 2, 4-6, 13-19, and 20-23 are indefinite because the phrase "the PCR product of the MC4R gene" lacks proper antecedent basis in the claims.

Claims 2, 4-6, 13-23, and 28 are indefinite over the recitation of "at base 678" or "nucleotide 678" because these claims are referring to a specific nucleotide position of a specific

PCR product, yet the claims do not include a step which produces the specific PCR product. Therefore, the claims suggest that nucleotide 678 of any PCR product is useful for screening for a polymorphism indicative of the metabolic traits in question. Claim 28 is further indefinite over the recitation of "a PCR product" for this same reason.

Claims 5 and 28 are indefinite over the recitation of "lower feed intake" because this is a relative term and the claim does not establish what the feed intake is lower than.

Claims 6 and 28 are indefinite over the recitation of "faster rate of gain" because this is a relative term and the claims do not establish what the rate of gain is faster than.

Claims 12, 14-19, and 27 are indefinite because they recite sequence identifiers which are not clearly defined in the specification. For example, the sequence labeled SEQ ID NO: 6 in the specification is different from the sequence labeled as SEQ ID NO: 6 in the sequence listing. It is not clear, therefore, which actual sequences are being claimed. This is a particular problem with respect to claims 19 and 27 since SEQ ID NO: 11 in the sequence listing is an amino acid sequence.

Claims 13-19 are indefinite over the language "consisting of a nucleotide sequence having" because this is an improper combination of both open and closed claim language since "consisting of" is closed claim language and "having" is open claim language. Therefore, it is not clear if applicant intends for the claim to be limited to sequences consisting of 4-30 nucleotides of SEQ ID NO: 1 or having 4-30 nucleotides of SEQ ID NO: 1. Furthermore, dependent claims 14-19 use open claim language "has" and therefore the claims are rendered even more confusing.

Claim 26 is indefinite over the recitation of "capable of amplifying" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited probes have the potential to amplify or do in fact amplify the MC4R. Amendment of the claim to read, for example, "which amplifies" would obviate this rejection.

Claim 28 is further indefinite because the phrase "the nucleotide associated with the desired traits" lacks proper antecedent basis in the claim.

Claims 29-30 are indefinite because they does not contain any method steps which clearly define the scope of the claimed invention. The claims do not clearly provide positive process steps. See MPEP 2173.05(q).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Studier *et al.* (US 5547843).

Studier *et al.* teach hexanucleotide primers useful for amplifying PCR products. Primer A1 taught by Studier *et al.* consists of the complement of nucleotides 23-28 of instant SEQ ID NO: 1. Primer B3 taught by Studier *et al.* consists of nucleotides 708-713 of instant SEQ ID NO: 1.

9. Claims 13, 24, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim 1997 Biochemicals Catalog.

The Boehringer catalog offers a kit comprising a primer mixture which comprises all possible hexanucleotide primers Catalog Number 1277081 (p. 122). These are primers which are useful for detecting nucleotide 678 of SEQ ID NO: 1.

10. Claims 1 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Yeo *et al.* (Nature Genetics, Vol. 20, October 1998, p. 111-112).

Yeo *et al.* teach a method for identifying a human which possesses a genotype indicative of the metabolic trait of fat content comprising obtaining a nucleic acid sample from the animal and identifying a polymorphism in the MC4R gene of the sample. The method comprises amplifying the MC4R gene (see Fig 1 legend).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 13, 14, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada *et al.* (US 5703220) in view of Hogan *et al.* (US 5595874).

This rejection refers to sequences using the sequence identifiers in the sequence listing.

Yamada *et al.* teaches the full length sequence of the human MC4R gene (SEQ ID NO: 7 in the disclosure of Yamada *et al.*). This sequence comprises instant SEQ ID NO: 6 (consisting of the complement of nucleotides 947-966 of Yamada's SEQ ID NO: 7), SEQ ID NO: 8 (consisting of nucleotides 477-495), and SEQ ID NO: 10 (consisting of the complement of SEQ ID NO: 939-960). It is noted that Yamada *et al.*'s disclosure of the human MC4R gene also comprises instant SEQ ID NO: 5 (as listed in the sequence listing) at nucleotides 200-219. Yamada *et al.* further teach DNA probes useful for detecting the MC4R gene, wherein such probes comprise a nucleic acid molecule of at least about 17-21 nucleotides (Col. 9, lines 19-24).

Yamada *et al.* do not teach fragments which consist of instant SEQ ID NO: 5, 6, 8, or 10.

However, at the time the invention was made, the prior art was replete with instruction and guidance as to how to select primers and probes. Hogan et al. (US 5595874) teach the use of specific primers and furthermore provides specific guidance for the selection of primers,

> "At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many

> destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line 13)."

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have selected smaller portions of the sequence taught by Yamada *et al.* that would have been useful as probes and primers. The ordinary practitioner would have been motivated to select these sequences by Yamada *et al.*'s teaching of probes for the detection of the gene in a sample. In the absence of a secondary consideration such as unexpected results, all of the smaller probes within the sequence taught by Yamada *et al.* are considered functional homologues with respect to their ability to prime nucleic acid amplification, including the instantly disclosed nucleic acid sequences.

14. Claims 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada *et al.* in view of Hogan *et al.* as applied to claims 13, 14, 16, and 18 above, and further in view of the Stratagene Catalog (1998).

Yamada *et al.* in view of Hogan *et al.* do not teach kits comprising the instantly disclosed reagents.

Stratagene teaches the benefits of kits in molecular biology. Stratagene teaches gene characterization kits. The ordinary practitioner would have been motivated to have produced

such a kit because since the Stratagene catalog expressly teaches the benefits to the practitioner of kits:

> "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, pre-mixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control."

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Therefore, the kits of the instant claims are *prima facie* obvious over the disclosure of Yamada *et al.* in view of Hogan *et al.* in view of the Stratagene catalog.

Conclusion

15. Nucleic acids consisting of instant SEQ ID NO: 7 and 9 (as disclosed in the sequence listing) are free of the prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

June 12, 2001